WEST Search History

DATE: Wednesday, September 04, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L7	liposome$ adj10 pyridox$	1	L7
L6	liposome$ adj5 pyridox$	1	L6
L5	L4 and liposome$	68	L5
L4	(fv adj1 antibod$)	208	L4
L3	liposomes same (fv adj1 antibod$)	0	L3
L2	L1 and peg	11	L2
L1	liposome$ same selectin	58	L1

END OF SEARCH HISTORY

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End of Result Set

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L2: Entry 11 of 11 File: USPT Sep 1, 1998

DOCUMENT-IDENTIFIER: US 5800815 A
TITLE: Antibodies to P-selectin and their uses

Detailed Description Text (96):
The P-selectin targeting may also be accomplished via amphipaths, or dual character molecules (polar:nonpolar) which exist as aggregates in aqueous solution. Amphipaths include nonpolar lipids, polar lipids, mono- and diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids and salts. These molecules can exist as emulsions and foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions and lamellar layers. These are generically referred to herein as liposomes. In these preparations, the drug to be delivered is incorporated as part of a liposome in which an anti-P-selectin immunoglobulin is embedded. In this embodiment, the immunoglobulin need not bind a functional epitope on the P-selectin molecule, so long as the immunoglobulin effectively targets the liposome to P-selectin molecules. When the liposomes are brought into proximity of the affected cells, they deliver the selected therapeutic compositions.

Detailed Description Text (154):
Four days after the final boost the spleen was removed and 1.2.times.10.sup.8 splenocytes were recovered. These were fused with FOX-NY myeloma cells using PEG 1500 (BMB) using the following protocol: The isolated splenocytes were washed twice in serum-free cell culture medium. Splenocytes and myeloma cells were combined at a ratio of 1:4.8 (myelomas to spleen cells). The combined cell pellet was washed twice in serum free medium, then aspirated to dryness. The cell pellet was resuspended by gentle tapping and heated in a waterbath at 37.degree. C. for 1 min. The pellet was distributed around the sides and bottom of a 50 ml conical centrifuge tube. One ml of PEG 1500 (50% w/v in 75 mM HEPES, BMB Lot #14702800) previously warmed to 37.degree. C. was added over 60 seconds while rotating the tube to maintain a thin layer of cells. One ml of serum free medium was added slowly over 60 seconds. An additional 1 ml of medium was added slightly faster. A further 8 ml of medium was added and the tube was allowed to stand undisturbed for 8 min and was then centrifuged for 5 min at 300xg. The final pellet was resuspended in RPMI 1640 containing 10% fetal bovine serum HYCLONE), 1% L-glutamine, 1% Sodium Pyruvate, and 1xAAT (SIGMA). The cells were plated in 10 flat bottom 96 well microtiter plates (COSTAR). No feeder cells were used.

Detailed Description Text (162):
Four days post final boost, the spleen was removed and the splenocytes were recovered. They were fused with FOX-NY myeloma calls using PEG 1500 (Sigma) generally as described in Oi et al., "Immunoglobulin-Producing Hybrid Cell Lines" in Selected Methods in Cellular Immunology, eds. Mishell and Shiigi, pp 351-372, 1980, which is incorporated herein by reference.

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L1: Entry 41 of 58 File: USPT Feb 18, 1997

DOCUMENT-IDENTIFIER: US 5604207 A
TITLE: Sialyl Le.sup.x analogues as inhibitors of cellular adhesion

Brief Summary Text (180):
The selectin receptor targeting can also be accomplished via amphipaths, or dual character molecules (polar:nonpolar) that exist as aggregates in aqueous solution. Amphipaths include nonpolar lipids, polar lipids, mono- and diglycerides, sulfatides, lysolecithin, phospholipids, sapchin, bile acids and salts. These molecules can exist as emulsions and foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions and lamellar layers. These are generically referred to herein as liposomes. In these preparations the drug to be delivered is incorporated as part of a liposome in conjunction with a SLe.sup.x analogue compound that binds to the selectin receptor.

Brief Summary Text (181):
A contemplated SLe.sup.x analogue compound whose R.sup.2 group is a C.sub.12 -C.sub.18 hydrocarbyl group is particularly useful in such liposome preparations. Thus, liposomes filled with a desired chemotherapeutic agent can be directed to a site of tissue injury by the selectin-SLe.sup.x analogue compound interaction. When the liposomes are brought into proximity of the affected cells, they deliver the selected therapeutic compositions.

Brief Summary Text (186):
Targeting mechanisms generally require that the targeting agents be positioned on the surface of the liposome in such a manner that the target agents are available for interaction with the selectin receptor. The liposome is typically fashioned in such a way that a connector portion is first incorporated into the membrane at the time of forming the membrane. The connector portion has a lipophilic portion that is firmly embedded and anchored in the membrane. It also has a hydrophilic portion that is chemically available on the aqueous surface of the liposome. The hydrophilic portion is selected so that it is chemically suitable to form a stable chemical bond with the targeting agent which is added later. Therefore, the connector molecule has both a lipophilic anchor and a hydrophilic reactive group suitable for reacting with the target agent and holding the target agent in its correct position, extended out from the liposome's surface. In some cases one can attach the target agent to the connector molecule directly, but in most instances it is more suitable to use a third molecule to act as a chemical bridge, thus linking the connector molecule which is in the membrane with the target agent which is extended, three dimensionally, off the vesicle surface.

Brief Summary Text (191):
The hydration medium contains the targeted drug at a concentration that is desired in the interior volume of the liposomes in the final liposome suspension. Typically the drug solution contains between 10-100 mg/mL in a buffered saline. The concentration of the targeting SLe.sup.x analogue compound which binds a selectin is generally between about 0.1-20 mg/mL.

L5: Entry 60 of 68 File: USPT Nov 24, 1998

DOCUMENT-IDENTIFIER: US 5840300 A
TITLE: Methods and compositions comprising single chain recombinant antibodies

Detailed Description Text (7):
Those of skill in the art of a particular disease and having an understanding of the nature of the target antigen will know how to make a single chain Fv antibody directed against that antigen following the procedures described herein. The preferred disease against which antibodies of the invention are directed is HIV-1 infection and/or AIDS. The preferred target antigen is HIV-1 gp120.

Detailed Description Text (8):
Generation of the Fv fragments of the invention is accomplished as follows. The well known Bluescript KS+ vector (Stratagene, La Jolla, Calif.) is modified in order to render it: suitable for expression of the Fv fragments of the invention. Gene VIII of M13 phage is incorporated into this vector such that the Fv fragments cloned therein are expressed on the surface of the phage. Next, the variable regions of heavy and light chains are combined by PCR-SOE which facilitates generation of a single chain library in a single step. This procedure also serves to simplify screening of clones so generated. The method is simple and effective for the expression of Fv antibody genes in vitro.

Detailed Description Text (17):
The antibodies of the invention may also be used as therapeutic agents for treatment of a disease state associated with the production of an antigen, which disease state is diminished or ablated when the subject antigen is bound to an appropriate antibody. Binding of antibody to antigen may occur in any cell, tissue or bodily fluid wherein antigen is expressed and into which the antibody is delivered. The antibody is delivered to the cell, tissue or bodily fluid of the patient using traditional routes of administration of such proteins in humans. Such proteins are administered to a human in one of the traditional modes (e.g., orally, parenterally, transdermally or transmucosally), in a sustained release formulation using a biodegradable biopolymer, or by on-site delivery using micelles, gels and liposomes, or rectally (e.g., by suppository or enema). The antibodies may be administered to the human in a dosage of 0.1 .mu.g/kg/day to 50 mg/kg/day, either daily or at intervals sufficient to ablate or diminish the disease state. Precise formulations and dosages may be determined using standard techniques, by a pharmacologist of ordinary skill in the art.

Detailed Description Text (70):
The data presented herein establish that the methods of the invention are simple and effective for the expression of Fv antibody genes in vitro. Single-chain Fv antibodies for HIV-1 may be useful for several reasons including their smaller size; the fact that they may expose antigen-binding sites potentially more efficiently; and the fact that high levels of expression of single chain Fv may be achieved by using phage surface expression vectors. Such recombinant molecules possess traditional antibody-based biological activities which are extremely valuable as investigational reagents and may give important insight into natural immunity.

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L4: Entry 33 of 68 File: USPT Aug 17, 1999

US-PAT-NO: 5939401
DOCUMENT-IDENTIFIER: US 5939401 A

TITLE: Cationic amphiphile compositions for intracellular delivery of therapeutic molecules

DATE-ISSUED: August 17, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Marshall; John	Milford	MA		
Harris; David J.	Lexington	MA		
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Scheule; Ronald K.	Hopkinton	MA		
Cheng; Seng H.	Wellesley	MA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Genzyme Corporation	Cambridge	MA			02

APPL-NO: 08/ 680354 [PALM]
DATE FILED: July 15, 1996

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/661,279 filed Jun. 10, 1996 and entitled Cationic Amphiphile Compositions for Intracellular Delivery of Therapeutic Molecules", itself a continuation-in-part of U.S. application Ser. No. 08/546,110 filed Oct. 20, 1995 and entitled "Cationic Amphiphiles Containing Dialkylamine Lipophilic Groups for Intracellular Delivery of Therapeutic Molecules", U.S. Pat. No. 5,719,131 itself a continuation-in-part of U.S. application Ser. No. 08/540,867 filed Oct. 11, 1995 and entitled "Cationic Amphiphiles Containing Steroid Lipophilic Groups for Intracellular Delivery of Therapeutic Molecules", U.S. Pat. No. 5,747,491 itself a continuation-in-part of U.S. application No. Ser. 08/352,479 entitled "Cationic Amphiphiles for Intracellular Delivery of Therapeutic Molecules", as filed on Dec. 9, 1994 U.S. Pat. No. 5,650,096. This application also claims the priority of (1) United States provisional patent application no. 60/004,344 identified as Express Mail Label TB798223107 US, filed Sep. 26, 1995 and entitled "Molecular Model of Cationic Lipid/DNA Complexes", and (2) United States provisional patent application no. 60/004,399 identified as Express Mail Label-EF109437051 US filed on Sep. 27, 1995 and entitled "Intravenous Delivery of Therapeutic Compositions for Gene Therapy". The complete text, claims and drawings of all of the above applications are incorporated herein by reference in their entirety.

INT-CL: [06] A61 K 9/127, A61 K 48/00, A61 K 38/00, C07 J 9/00

US-CL-ISSUED: 514/44; 514/2, 424/450, 552/544
US-CL-CURRENT: 514/44; 424/450, 514/2, 552/544

FIELD-OF-SEARCH: 514/44, 514/2, 552/544, 424/450, 252/357, 935/52, 935/54

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5023087	June 1991	Yau-Young	424/450
☐	5459127	October 1995	Felgner et al.	514/7
☐	5614503	March 1997	Chaudhany et al.	514/44
☐	5747471	May 1998	Siegel et al.	514/44

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO 91/16024	October 1991	WO	
WO 93/05162	March 1993	WO	
WO 93/24640	December 1993	WO	
WO 94/21115	September 1994	WO	
WO 96/17823	June 1996	WO	
WO 96/18372	June 1996	WO	
WO 96/25508	August 1996	WO	
WO 96/32102	October 1996	WO	
WO 97/29118	August 1997	WO	
WO 97/31934	September 1997	WO	
WO 97/45442	December 1997	WO	

OTHER PUBLICATIONS

Gao et al (1991) Bio Chem Biophys Res. Comm. 179:280-285.
Felgner et al (1987) Proc. Natl. Acad. Sci, USA 84:7413-7417.
PV Gogineni et al (1993) Journal of Chromatography Biomedical Applications 620: 83-88.
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Bennett et al., "Cholesterol Enhances Cationic Liposome-Mediated DNA Transfection of Human Respiratory Epithelial Cells," Bioscience Reports, vol. 15, No. 1 (1995).
Li et al., "DC-Chol Lipid System in Gene Transfer," Journal of Controlled Release, 39, 373-381 (1996).
Behr et al., "Efficient Gene Transfer into Mammalian Primary Endocrine Cells with Lipopolyamine-coated DNA," Proc. Natl. Acad. Sci., vol. 86, pp. 6982-6986 (1989).
Egilmez et al., "Evaluation and Optimization of Different Cationic Liposome Formulations for in Vivo Gene Transfer," Biochemical and Biophysical Research Communication, 221, 169-173 (1996).
Guo et al., "Cationic Liposome Containing Noncytotoxic Phospholipid and Cholesterol Derivatives," Journal of Liposomes Research, 3(1), pp. 51-70 (1993).
Moradpour et al., "Efficient Gene Transfer into Mammalian Cells with Cholesteryl-Spermidine," Biochemical and Piophysical Research Communications, 221, pp. 82-88 (1986).
Takeuchi et al., "Effect of Zeta Potential of Cationic Liposomes Containing Cationic Cholesterol Deratives on Gene Transfection," FEBS Letters, 397, pp. 207-209 (1996).
Liu et al., "New Cationic Lipid Formulations for Gene Transfer," Pharmaceuticals Research, vol. 13, No. 12 (1996).

Lee et al., "Detailed Analysis of Structures and Formulations of Cationic Lipids for Efficient Gene Transfer to the Lung," Human Gene Therapy, 7, pp. 1701-1717 (1996).
Vigneron et al., "Guanidinium-cholesterol Cationic Lipids: Efficient Vectors for the Transfection of Eukaryotic Cells," Proc. Natl. Acad. Sci., vol. 93, pp. 9682-9686 (1996).
Weignberg, Robert A., "Retinoblastoma Protein and Cell Cycle Control," Cell, vol. 81, pp. 323-330 (1995).

ART-UNIT: 162

PRIMARY-EXAMINER: Campell; Bruce R.

ABSTRACT:

Novel cationic amphiphiles are provided that facilitate transport of biologically active (therapeutic) molecules into cells. By this invention, such cationic amphiphile is used in a state in which it is capable of accepting additional protons, i.e., it is not fully protonated. For purposes of this invention, cationic amphiphiles may be considered to encompass four general categories: (A) T-shaped/steroid-based amphiphiles; (B) T-shaped/non steroid-based amphiphiles; (C) non T-shaped/steroid based amphiphiles and (D) non T-shaped/non steroid-based amphiphiles.

5 Claims, 22 Drawing figures

L4: Entry 35 of 68 File: USPT Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5885613 A
TITLE: Bilayer stabilizing components and their use in forming programmable fusogenic liposomes

Drawing Description Text (7):
FIG. 5 illustrate the ability of PEG-Ceramide to act as a bilayer stabilizing component. Multilamellar vesicles were prepared, as described in the examples, from DOPE:cholesterol:egg ceramide-PEG.sub.2000 at a ratio of A, 1:1:0.1 or B, 1:1:0.25. Other conditions were the same as for FIG. 2.

Drawing Description Text (11):
FIG. 9 illustrates the inhibition of fusion by PEG-PE. Liposomes were prepared from equimolar mixtures of DOPE and POPS containing (a) 0; (b) 0.5; (c) 1 or (d) 2 mol % DMPE-PEG.sub.2000. In addition to the above lipids, labelled liposomes also contained the fluorescent lipids NBD-PE and Rh-PE at 0.5 mol %. Fluorescently labelled liposomes (final concentration 60 .mu.M were incubated at 37.degree. C. for 30 s before the addition of a three-fold excess of unlabelled liposomes, followed one minute later by CaCl.sub.2 (final concentration 5 mM).

Drawing Description Text (12):
FIG. 10 illustrates the recovery of fusogenic activity after PEG-PE removal. Fusion between fluorescently labelled and unlabelled liposomes containing 2 mol % DMPE-PEG.sub.2000 was assayed as described under FIG. 9, except that one minute after addition of CaCl.sub.2, a 12-fold excess (over labelled vesicles) of POPC liposomes (curve a) or an equivalent volume of buffer (curve b) was added.

Drawing Description Text (15):
FIGS. 13A and 13B illustrate the effect of PEG molecular weight on fusion. (A) Assays were carried out as described in FIG. 9 using liposomes which contained (a) 0; (b) 0.25; (c) 0.5 or (d) 1 mol % DMPE-PEG.sub.5000 ; and (B) Assays were performed as described under FIG. 12 using liposomes which contained 1 mol % DMPE-PEG.sub.5000 (.circle-solid.); DPPE-PEG.sub.5000 (.diamond-solid.) or DSPE-PEG.sub.5000 (.tangle-solidup.).

Drawing Description Text (18):
FIG. 16 illustrates the inhibition of fusion of DOPE:DODAC liposomes by PEG-PE. Liposomes were prepared from either DOPE:DODAC (85:15) or DOPE:DODAC:DMPE-PEG.sub.2000 (83:15:2). Fusion was assayed as described under FIG. 1 using 300 mM NaCl.

Drawing Description Text (19):
FIG. 17 illustrates the recovery fusogenic activity after PEG removal. Liposomes were prepared from either DOPE:DODAC:ceramide(C8:0)-PEG.sub.2000, 83:15:2 or DOPE:cholesterol:ceramide(C8:0)-PEG.sub.2000, 38:45:15:2. Fusion was assayed as described under FIG. 2 except that at the indicated times a 30 fold excess (over donors) of liposomes composed of POPC or POPC:cholesterol (55:45) was added.

Drawing Description Text (20):
FIG. 18 illustrates the effect of the lipid anchor on the rate of PEG-lipid removal. Fluorescently labelled and unlabelled liposomes were prepared from DOPE:DODAC:PEG-lipid, 83:15:2, using DMPE-PEG.sub.2000 (.circle-solid.), ceramide(egg)-PEG.sub.2000 or (C14:0) ceramide-PEG.sub.2000 (.diamond-solid.).

Labelled liposomes were mixed with a 3 fold excess of unlabelled liposomes and 300 mM NaCl in a cuvette in a dark water bath at 37.degree. C. At zero time a 13-fold excess (over labelled vesicles) of POPC liposomes was added and the fluorescence intensity was measured at the indicated times. At the end of the assay Triton X-100 (0.5% final) was added to eliminate energy transfer and the % fusion was calculated from the change in efficiency of energy transfer. Maximum fusion was calculated from a standard curve of energy transfer efficiency against the molar fraction of Rh-PE in the membrane assuming complete mixing of labelled and unlabelled liposomes.

Drawing Description Text (21):
FIG. 19 illustrates the inhibition of fusion between DOPE:cholesterol:DODAC liposomes and anionic liposomes by PEG-ceramide. Liposomes were prepared from DOPE:cholesterol:DODAC, 40:45:15 (no PEG) or DOPE:cholesterol:DODAC:(C14:0) ceramide-PEG.sub.2000, 36:45:15:4 (4% PEG). Acceptor liposomes were prepared from DOPE:cholesterol:POPS, 25:45:30. A three-fold excess of acceptors was added to labelled vesicles after 30 s and the fluorescence monitored at 517 nm with excitation at 465 nm.

Drawing Description Text (22):
FIG. 20 illustrates the recovery of fusogenic activity upon PEG removal. Donor liposomes (50 .mu.M) were prepared from DOPE:cholesterol:DODAC:(C14:0)ceramide-PEG.sub.2000, 36:45:15:4 and mixed with acceptor liposomes (150 .mu.M) prepared from DOPE:cholesterol:POPS, 25:45:30. At zero time either 1 mM POPC:cholesterol liposomes (.tangle-solidup.) or an equivalent volume of buffer (.circle-solid.) was added. Fluorescence was monitored at 517 nm with excitation at 465 nm.

Drawing Description Text (23):
FIG. 21 illustrates the inhibition of fusion between DOPE:cholesterol:DODAC liposomes and erythrocyte ghosts by, PEG-ceramide. Liposomes were prepared from DOPE:cholesterol:DODAC, 40:45:15 (no PEG) or DOPE:cholesterol:DODAC:(C14:0)ceramide-PEG.sub.2000, 36:45:15:4 (4% PEG). Ghosts (50 .mu.M phospholipid) were added to donors (50 .mu.M total lipid) after 30 s and the fluorescence monitored at 517 nm with excitation at 465 nm.

Drawing Description Text (24):
FIGS. 22A-22F illustrate the fusion of fluorescent liposomes composed of DOPE:cholesterol:DODAC (40:45:15) or DOPE:cholesterol:DODAC:PEG-ceramide (35:45:15:5). LUVs composed of DOPE:cholesterol:DODAC (40:45:15) fused with RBCs (panels a and b); incorporation of PEG-ceramide (C8:0) into the LUVs at 5 mol % blocked fusion (panels c and d); however, when an exogenous sink for the PEG-ceramide was included, fusogenic activity was recovered within minutes (panels e and f). Panels a, c and e are views under phase contrast, and panels b, d and f are the same fields view under fluorescent light.

Drawing Description Text (25):
FIGS. 23A-23F illustrate the results when PEG-ceramides with longer fatty amide chains (C14:0) are used and the liposomes are pre-incubation with an exogenous sink prior to the addition of the RBCs. No fusion was observed after pre-incubation of the fusogenic LUVs with the sink for five minutes prior to addition of RBC (panels a and b); after a 1 hour pre-incubation, some fusion with RBCs was observed (panels c and d); however, with longer incubations times (2 hours), the pattern of fluorescent labeling changed and extensive punctate fluorescence was observed (panels e and f). Panels a, c and e are views under phase contrast, and panels b, d and f are the same fields view under fluorescent light.

Drawing Description Text (26):
FIGS. 24A-24F illustrate the results when PEG-ceramides with longer fatty amide chains (C20:0) are used and the liposomes are preincubation with an exogenous sink prior to the addition of the RBCs. No fusion was observed after pre-incubation of the LUVs with the sink for five minutes (panels a and b), 1 hour (panels c and d) or 2 hours (panels e and f). Panels a, c and e are views under phase contrast, and panels b, d and f are the same fields view under fluorescent light.

Detailed Description Text (12):

In addition to the foregoing, detergents, proteins and peptides can be used as bilayer stabilizing components. Detergents which can be used as bilayer stabilizing components include, but are not limited to, Triton X-100, deoxycholate, octylglucoside and lyso-phosphatidylcholine. Proteins which can be used as bilayer stabilizing components include, but are not limited to, glycophorin and cytochrome oxidase. Cleavage of the protein, by endogenous proteases, resulting in the loss of the bulky domain external to the bilayer would be expected to reduce the bilayer stabilizing ability of the protein. In addition, peptides which can be used as bilayer stabilizing components include, for example, the pentadecapeptide, alanine-(aminobutyric acid-alanine).sub.14. This peptide can be coupled, for example, to polyethyleneglycol which would promote its transfer out of the bilayer. Alternatively, peptides such as cardiotoxin and melittin, both of which are known to induce non-lamellar phases in bilayers, can be coupled to PEG and might thereby be converted to bilayer stabilizers in much the same way that PE is converted from a non-lamellar phase preferring lipid to a bilayer stabilizer when it is coupled to PEG. If the bond between the peptide and the PEG is labile, then cleavage of the bond would result in the loss of the bilayer stabilizing ability and in the restoration of a non-lamellar phase, thereby causing the liposome to become fusogenic.

Detailed Description Text (16):
A variety of methods are available for preparing liposomes as described in, e.g., Szoka et al., Ann. Rev. Biophys. Bioeng. 9:467 (1980), U.S. Pat. Nos. 4,186,183, 4,217,344, 4,235,871, 4,261,975, 4,485,054, 4,501,728, 4,774,085, 4,837,028, 4,235,871, 4,261,975, 4,485,054, 4,501,728, 4,774,085, 4,837,028, 4,946,787, PCT Publication No. WO 91.backslash.17424, Deamer and Bangham, Biochim. Biophys. Acta, 443:629-634 (1976); Fraley, et al., Proc. Natl. Acad. Sci. USA 76:3348-3352 (1979); Hope, et al., Biochim. Biophys. Acta 812:55-65 (1985); Mayer, et al., Biochim. Biophys. Acta 858:161-168 (1986); Williams, et al., Proc. Natl. Acad. Sci. USA 85:242-246 (1988); the text Liposomes, (Marc J. Ostro (ed.), Marcel Dekker, Inc., New York, 1983, Chapter 1); and Hope, et al., Chem. Phys. Lip. 40:89 (1986), all of which are incorporated herein by reference. Suitable methods include, for example, sonication, extrusion, high pressure/homogenization, microfluidization, detergent dialysis, calcium-induced fusion of small liposome vesicles and ether-fusion methods, all of which are well known in the art. One method produces multilamellar vesicles of heterogeneous sizes. In this method, the vesicle-forming lipids are dissolved in a suitable organic solvent or solvent system and dried under vacuum or an inert gas to form a thin lipid film. If desired, the film may be redissolved in a suitable solvent, such as tertiary butanol, and then lyophilized to form a more homogeneous lipid mixture which is in a more easily hydrated powder-like form. This film is covered with an aqueous buffered solution and allowed to hydrate, typically over a 15-60 minute period with agitation. The size distribution of the resulting multilamellar vesicles can be shifted toward smaller sizes by hydrating the lipids under more vigorous agitation conditions or by adding solubilizing detergents such as deoxycholate.

Detailed Description Text (22):
Cationic lipids have been used in the transfection of cells in vitro and in vivo (Wang, C-Y, Huang L., "pH sensitive immunoliposomes mediate target cell-specific delivery and controlled expression of a foreign gene in mouse," Proc. Natl. Acad. Sci. USA, 1987; 84:7851-7855 and Hyde, S. C., Gil, D. R., Higgins, C. F., et al., "Correction of the ion transport defect in cystic fibrosis transgenic mice by gene therapy," Nature, 1993; 362:250-255). The efficiency of this transfection has often been less than desired, for various reasons. One is the tendency for cationic lipids complexed to nucleic acid to form unsatisfactory carriers. These carriers are improved by the inclusion of PEG lipids.

Detailed Description Text (34):
The cells of the host are usually exposed to the liposomal preparations of the invention by in vivo administration of the formulations, but ex vivo exposure of the cells to the liposomes is also feasible. In vivo exposure is obtained by administration of the liposomes to host. The liposomes may be administered in many ways. These include parenteral routes of administration, such as intravenous, intramuscular, subcutaneous, and intraarterial. Generally, the liposomes will be administered intravenously or in some cases via inhalation. Often, the liposomes will be administered into a large central vein, such as the superior vena cava or inferior

vena cava, to allow highly concentrated solutions to be administered into large volume and flow vessels. The liposomes may be administered intraarterially following vascular procedures to deliver a high concentration directly to an affected vessel. In some instances, the liposomes may be administered orally or transdermally, although the advantages of the present invention are best realized by parenteral administration. The liposomes may also be incorporated into implantable devices for long duration release following placement.

Detailed Description Text (35):
As described above, the liposomes will generally be administered intravenously or via inhalation in the methods of the present invention. Often multiple treatments will be given to the patient. The dosage schedule of the treatments will be determined by the disease and the patient's condition. Standard treatments with therapeutic compounds that are well known in the art may serve as a guide to treatment with liposomes containing the therapeutic compounds. The duration and schedule of treatments may be varied by methods well known to those of skill, but the increased circulation time and decreased in liposome leakage will generally allow the dosages to be adjusted downward from those previously employed. The dose of liposomes of the present invention may vary depending on the clinical condition and size of the animal or patient receiving treatment. The standard dose of the therapeutic compound when not encapsulated may serve as a guide to the dose of the liposome-encapsulated compound. The dose will typically be constant over the course of treatment, although in some cases the dose may vary. Standard physiological parameters may be assessed during treatment that may be used to alter the dose of the liposomes of the invention.

Detailed Description Text (36):
Liposome charge is an important determinant in liposome clearance from the blood, with negatively charged liposomes being taken up more rapidly by the reticuloendothelial system (Juliano, Biochem. Biophys. Res. Commun. 63:651 (1975)) and, thus, having shorter half-lives in the bloodstream. Liposomes with prolonged circulation half-lives are typically desirable for therapeutic and diagnostic uses. To maximize circulation half-lives, the bilayer stabilizing component should be a hydrophilic polymer, e.g., PEG, conjugated to lipid anchors, e.g., PEs, having long, saturated hydrocarbon chains (C18>C16>C14) as these conjugates provide a longer lasting steric barrier. As such, by varying the charge in addition to the foregoing factors, one of skill in the art can regulate the rate at which the liposomes of the present invention become fusogenic.

Detailed Description Text (42):
All phospholipids including fluorescent probes and PEG-PE conjugates were purchased from Avanti Polar Lipids, Birmingham, Alabama, USA.
1-O-methyl(poly(ethoxy)-O-succinyl-O-(egg)ceramide which was a gift from Dr L. Choi of Inex Pharmaceuticals Corp., Vancouver, BC, Canada. Di-[1-.sup.14 C]-palmitoylphosphatidylcholine was purchased from Du Pont, Mississuaga, Ont., Canada. [.sup.3 H]-DSPE-PEG.sub.2000 was synthesized as described previously (Parr, et al., Biochim. Biophys. Acta, 1195: 21-30 (1994)). Other reagents were purchased from Sigma Chemical Co., St Louis, Mo., USA.

Detailed Description Text (53):
Lipid mixing was measured by a modification of the fluorescence resonance energy transfer (FRET) assay of Struck, et al. (Biochemistry 20:4093-4099 (1981)). LUVs were prepared containing the fluorescent lipids, N-(7-nitro-2-1,3-benzoxadiazol-4-yl)dioleoylphosphatidylethanolamine (NBD-PE) and N-(lissamine rhodamine B sulfonyl)-dipalmitoylphosphatidylethanolamine (Rh-PE) at 0.5 mol %. LUVs (50-60 .mu.M) and a three-fold excess of unlabelled target vesicles were mixed in the fluorimeter at 37.degree. C. for short term assays (.ltoreq.1 hour), or in sealed cuvettes in a dark water bath at 37.degree. C. for longer assays. For measurements of fusion after PEG-lipid transfer, an excess of liposomes prepared from 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) was added as a sink for the PEG-lipid. Fluorescence emission intensity was measured at 517 nm with excitation at 465 nm both before and after the addition of Triton X-100 (final concentration of 0.5% or 1% when POPC sink was used). Data is presented as either uncorrected fluorescence intensity for short term assays (.ltoreq.1 hour) or as percentage fusion. Light scattering controls were performed by replacing LUVs labelled with 0.5 mol % probes with unlabelled vesicles. Maximum fusion was determined using mock fused

vesicles containing 0.125 mol % of each fluorescent probe. The percentage fusion was calculated as: ##EQU1## where F.sub.(t) =fluorescence intensity at time t; F.sub.o =fluorescence intensity at zero time; F.sub.T =fluorescence intensity in the presence of Triton X-100. M and L represent the same measurements for the mock fused control and the light scattering control respectively. Changes in fluorescence of the mock fused control indicated that exchange of the fluorescent probes over 24 hours accounted for 10% of the fluorescence change observed, but was negligible over the first hour.

Detailed Description Text (55):
LUVs composed of DOPE:cholesterol:DODAC (40:45:15) or DOPE:cholesterol:DODAC:PEG-ceramide (35:45:15:) were prepared by standard extrusion techniques. LUVs also contained 1 mol % rhodamine-PE. LUVs (200 .mu.M) were incubated at 37.degree. C. with 50 .mu.l packed RBCs in a final volume of 1 ml. For assays of fusion after PEG-lipid exchange, a sink of 2 mM POPC:cholesterol (55:45) was included. In some assays, the fusogenic liposomes were pre-incubated with the sink before being mixed with the RBCs (See, figure legends for FIGS. 22-24). Aliquots of the mixtures were transferred to glass microscope slides, covered with cover slips and examined by phase contrast and fluorescent microscopy. Fusion was assessed as fluorescent labeling of the RBC plasma membranes. For FIGS. 22-24, fluorescent liposomes were incubated with POPC:cholesterol liposomes and/or RBCs as described in section "L," infra. Panels a, c and e of FIGS. 22-24 are views under phase contrast, whereas panels b, d and f of FIGS. 22-24 are the same fields viewed under fluorescent light.

Detailed Description Text (69):
E. The use of PEG-ceramides as bilayer stabilizing components

Detailed Description Text (70):
The spectra set forth in FIGS. 1-4 were all obtained using PEG conjugated to phosphatidylethanolamine through a carbamate linkage. In addition, however, the use of ceramide as an alternative anchor for the hydrophilic polymer was examined. PEG.sub.2000 was conjugated via a succinate linker to egg ceramide. FIG. 5 shows the .sup.31 P-NMR spectra obtained using mixtures of DOPE:cholesterol:egg ceramide-PEG.sub.2000 (1:1:0.1 and 1:1:0.25) over the temperature range of 0.degree. to 60.degree. C. At the lower molar ratio of PEG-ceramide, both bilayer and H.sub..PI. phase lipid are in evidence at most temperatures. However, at the higher PEG-ceramide molar ratio, the spectra are exclusively bilayer up to 60.degree. C. at which point a low field shoulder corresponding to H.sub..PI. phase lipid is visible. Unlike the spectra obtained using PEG-PEs, there was almost no isotropic signal when PEG-ceramide was used.

Detailed Description Text (75):
The presence of lipid micelles is not readily apparent from freeze fracture electron microscopy. Lipid in the micellar phase could, however, contribute to the isotropic signal observed in NMR spectra, and it has previously been shown that PEG-PE conjugates form micelles when hydrated in isolation (Woodle and Lasic, Biochim. Biophys. Acta, 113:171-199 (1992)). As such, the presence of micelles was tested by subjecting a suspension of LUVs to molecular sieve chromatography on Sepharose 4B. The liposomes were of the same composition used for the freeze fracture studies above except that DSPE-PEG.sub.2000 was used in place of DOPE-PEG.sub.2000, and they contained trace amounts of .sup.14 C-DPPC and .sup.3 H-DSPE-PEG.sub.2000. The elution profile is shown in FIG. 8. A single peak containing both the phospholipid and PEG-PE conjugate markers was found in the void volume. A control experiment also shown in FIG. 8 demonstrated that micelles, which formed when PEG-PE was hydrated in isolation, were included into the column and would have been clearly resolved if present in the liposomal preparation.

Detailed Description Text (78):
H. The effect of PE-PEG loss on fusion

Detailed Description Text (79):
Recently, it has been demonstrated that phospholipids conjugated to PEG of molecular weights 750-5,000 Da have enhanced rates of spontaneous transfer between liposomes. The half-time for transfer of these conjugates can vary from minutes to hours and

depends on both the size of the PEG group and the nature of the acyl chains which anchor the conjugate in the bilayer. As such, fusion was examined under conditions where the PEG-lipid would be expected to transfer out of the liposomes. Ca.sup.2+ ions were added to PE:PS liposomes containing 2 mol % DMPE-PEG.sub.2000, followed by a twelve-fold excess (over labelled vesicles) of 1-paimitoyl-2-oleoyl-phosphatidylcholine (POPC) liposomes as a sink for the PEG-PE. As shown in FIG. 10 (curve a), while fusion was initially blocked by the presence of DMPE-PEG.sub.2000, the addition of POPC liposomes, which acted as a sink, lead to recovery of full fusogenic activity following a short time lag. The small initial jump in fluorescence intensity that occurred when POPC liposomes were added to PE:PS liposomes resulted from increased light scattering, not fusion. Control experiments demonstrated that no fusion occurred between the PE:PS liposomes and the POPC liposomes (data not shown), and no fusion occurred in the absence of POPC liposomes (FIG. 10, curve b).

Detailed Description Text (80):
To confirm that recovery of fusogenic activity was dependent on removal of the PEG-PE, the influence of initial PEG-lipid concentration on the duration of the lag phase prior to fusion was examined (FIG. 11). Liposomes containing equimolar PE and PS were prepared with 2, 3, 5 or 10 mol % DMPE-PEG.sub.2000. Fluorescently labelled and unlabelled vesicles were mixed at a ratio of 1:3 and after the addition of 5 mM CaCl.sub.2, a 36fold excess (over labelled vesicles) of POPC liposomes was added. As expected, there was an increase in the time delay prior to fusion with increasing PEG-lipid concentration.

Detailed Description Text (82):
Since fusion is dependent on prior transfer of the PEG-PE out of the liposomes, it was thought that the rate at which fusogenic activity was recovered would depend on the rate of transfer of the PEG-PE. One factor that affects the rate at which a phospholipid transfers from one membrane to another is the length of its acyl chains. As such, the effect of conjugate acyl chain composition on fusogenic activity was investigated. In doing so, the recovery of fusogenic activity of PE:PS LUVs containing 2 mol % DMPE-PEG.sub.2000 was compared with PE:PS LUVs containing 2 mol % DPPE-PEG.sub.2000 and 2 mol % DSPE-PE.sub.2000 (FIG. 12A). Increasing the length of the acyl chains from 14 to 16 carbons caused a dramatic increase in the lag period before fusion was initiated. Although the same level of fusion occurred using either DMPE-PEG.sub.2000 or DPPE-PEG.sub.2000, it was essentially complete in 40 minutes when DMPE-PEG.sub.2000 was the stabilizer, but took 24 hours when DPPE-PEG.sub.2000 was used. The implied decrease in rate of transfer (30-40 fold) is consistent with previous measurements of the effect of acyl chain length on rates of spontaneous phospholipid transfer. Increasing the acyl chain length to 18 carbons (DSPE-PEG.sub.2000, FIG. 12A) extended the lag in fusion even further and, after 24 hours, the level was only 20% of maximum.

Detailed Description Text (83):
A second factor that affects the rate of spontaneous transfer of phospholipids between bilayers is the degree of saturation or unsaturation of the acyl chains. The rate of fusion of LUVs containing 2 mol % DOPE-PEG.sub.2000 is shown in FIG. 12B. The presence of a double bond increased the rate of recovery of fusogenic activity in the presence of a sink for the DOPE-PEG.sub.2000 over that of the corresponding saturated species (DSPE-PEG.sub.2000, FIG. 12A). The rate of fusion was similar to that seen with DPPE-PEG.sub.2000. FIG. 12B also shows the rate of fusion obtained when the neutral PEG-lipid species, egg ceramide-PEG.sub.2000 was used. The rate was somewhat faster than observed with DPPE-PEG.sub.2000. Although differences in the interaction of the two lipid anchors with neighboring phospholipids in the bilayer make direct comparison of interbilayer transfer rates and, hence, fusion difficult, it appears that the presence of a negative charge on the conjugate (PE-PEG) is not required for desorption of the conjugate from negatively charged bilayers.

Detailed Description Text (84):
J. Effect of PEG molecular weight on fusogenic activity

Detailed Description Text (85):
The presence of PEG conjugated to the liposome surface results in a steric barrier that inhibits close bilayer apposition and subsequent fusion. The magnitude of the

barrier should increase with increasing PEG molecular weight. When DMPE-PEG.sub.5000 was incorporated into PE:PS (1:1) LUVS, a concentration dependent inhibition of fusion was observed (FIG. 13A). The results are similar to those obtained with DMPE-PEG.sub.2000 (FIG. 9), except that only 1 mol % DMPE-PEG.sub.5000 was required to completely inhibit fusion compared to 2 mol % DMPE-PEG.sub.2000.

Detailed Description Text (86):
FIG. 13B shows the effect of varying acyl chain composition of the larger PEG-lipid conjugate on fusion. Interestingly, the rates of fusion observed with 1 mol % PE-PEG.sub.5000 were similar to those with 2 mol % PE-PEG.sub.2000. The concentrations used were those shown to be sufficient to completely inhibit fusion (cf., FIG. 9 and FIG. 13A). It was thought that the larger PEG group would increase the rate of interbilayer transfer of the conjugate and, hence, the rate of fusion. However, this was not the case. To examine this aspect further, the rates of fusion under conditions where the initial surface density of ethylene glycol groups was similar were compared. FIG. 14 shows the fusion of PE:PS (1:1) LUVs containing 5 mol % DMPE-PE.sub.2000 or 2 mol % DMPE-PEG.sub.5000 after addition of a sink for the PEG-lipid. The rates observed were very similar suggesting that factors other than loss of the steric barrier as a direct result of interbilayer transfer of the conjugate were involved.

Detailed Description Text (89):
As described above, the inclusion of 2 mol % PEG-lipid in PE:PS liposomes is sufficient to inhibit Ca.sup.2+ -induced fusion. When 2 mol % DMPE-PEG.sub.2000 was included in DOPE:DODAC liposomes (DOPE:DODAC:DMPE-PEG.sub.2000, 83:15:2), the same inhibitory effect was observed (FIG. 16). However, unlike the PE:PS system, when these liposomes were incubated for 1 hr in the presence of a large excess of POPC liposomes, which acted as a sink for the PEG-PE, little, if any, fusion was observed. Since PEG-PEs are negatively charged the complementary charge, interaction with DODAC likely results in a dramatic decrease in the rate of transfer out of the bilayer.

Detailed Description Text (90):
As an alternative bilayer stabilizing component, therefore, the ability of a neutral PEG-lipid species, i.e., PEG-ceramide, to inhibit fusion in this system was examined. PEG-ceramides have similar bilayer stabilizing properties to PEG-PEs. For these studies, PEG.sub.2000 was conjugated to ceramides of various fatty amide chain lengths through a succinate linker. Liposomes prepared from DOPE:DODAC:(C8:0) ceramide-PEG.sub.2000 (83:15:2) did not fuse in the presence of 300 mM NaCl. However, when an excess of POPC liposomes was added, fusion occurred fairly rapidly (FIG. 17). Similar results were observed when cholesterol was incorporated into the liposomes (DOPE:cholesterol:DODAC:(C8:0) ceramide-PEG.sub.2000, 38:45:15:2), although the rate of fusion was slower than with cholesterol-free liposomes (FIG. 17).

Detailed Description Text (91):
To determine if the rate of fusion in this system can be controlled, the chain lengths of the fatty amide groups of the PEG-ceramides were varied. Using a (C14:0) ceramide-PEG.sub.2000, 50% maximal fusion was observed after approximately 6 hr (FIG. 18). This was a dramatic increase over the rate with (C8:0) ceramide-PEG.sub.2000 shown in FIG. 18, where maximal fusion was achieved in about 40 minutes. The time for 50% maximal fusion was increased to over 20 hr when egg ceramide-PEG.sub.2000 was used. Ceramides derived from egg have a fatty amide chain length of predominantly 16:0 (approximately 78%), with small amounts of longer saturated chains. FIG. 18 also shows an extended time course with DMPE-PEG.sub.2000. The limited extent of fusion (<20% of maximum at 21 hr) shows the dramatic effect that charge interaction can have on PEG-lipid transfer rates.

Detailed Description Text (92):
The rationale for using cationic liposomes is that complementary charge interaction with anionic plasma membranes will promote association and fusion of liposomes with cells in vivo. It is important, therefore, to confirm that not only will DOPE:DODAC liposomes fuse with membranes carrying a negative charge, but that incorporation of PEG-lipid conjugates prevents fusion in a programmable manner. This ability is demonstrated in FIG. 19 which shows that liposomes composed of DOPE:cholesterol:DODAC, 40:45:15, fuse with negatively charged liposomes and inclusion of a PEG-lipid conjugate in the cationic liposomes inhibits fusion. Fusion

between DOPE:DODAC liposomes could be prevented when 2 mol % PEG-lipid was present in both fluorescently labelled and acceptor liposomes. When PEG-lipid was omitted from the acceptor liposomes, however, its concentration in the labelled vesicles had to be increased to 4-5 mol % to block fusion between cationic and anionic liposomes.

Detailed Description Text (93):
Again, while PEG-lipids can inhibit fusion in this system, under conditions where the PEG-lipid can transfer out of the liposomes, fusogenic activity can be restored. FIG. 20 shows that this is, indeed, the case. Incubation of DOPE:cholesterol: DODAC:(C14:0) ceramide-PEG.sub.2000 (36:45:15:4) liposomes with PE:PS liposomes, in the presence of excess POPC:cholesterol (55:45) vesicles which act as a sink, results in recovery of fusogenic activity. In the absence of a sink, a slow rate of fusion is observed, indicating that a higher concentration of PEG-lipid is required to completely prevent fusion over longer periods.

Detailed Description Text (94):
While fusion between cationic and anionic liposomes provides a good model system, fusion in vivo is somewhat different. The acceptor membrane is not composed solely of lipid, but contains a high concentration of proteins, many of which extend outward from the lipid bilayer and may interfere with fusion. Using erythrocyte ghosts as a representative membrane system, it was found that liposomes composed of DOPE:cholesterol:DODAC (40:45:15) fuse with cellular membranes (see, FIG. 21). In addition, it was found that fusion in this system, like those presented above, can also be inhibited using PEG-lipid conjugates. This results clearly establish the usefulness of these systems as programmable fusogenic carriers for intracellular drug delivery.

Detailed Description Text (96):
LUVs composed of DOPE:cholesterol:DODAC (40:45:15) fused rapidly and extensively with RBCs (FIG. 22, panels a and b). Prolonged incubation caused extensive lysis of the RBCs and numerous fluorescently labeled "ghosts" were formed. Incorporation of PEG-ceramide (C8:0) at 5 mol % blocked fusion (FIG. 22, panels c and d) and this effect was maintained for up to 24 hr. This effect was somewhat surprising since the (C8:0) ceramide can exchange rapidly (i.e., within minutes) between liposomal membranes. It appears that either the RBCs cannot act as a sink for the PEG-ceramide, or there were insufficient RBCs to remove enough PEG-ceramide to allow fusion. However, when an exogenous sink for the PEG-ceramide was included, fusogenic activity was recovered within minutes (FIG. 22, panels e and f).

Detailed Description Text (97):
When PEG-ceramides with longer fatty amide chains (i.e., C14:0 or C20:0) were used, there was little fusion over 24 hr, even in the presence of an exogenous sink. This again was surprising as substantial fusion is observed over this time frame in liposomal systems when a sink is present. It was thought that some nonspecific interaction between the sink (POPC/cholesterol) and the RBCs was occurring which hindered the ability of the POPC:cholesterol liposomes to absorb the PEG-ceramide. To overcome this, the fusogenic liposomes were pre-incubated with the sink before adding RBCS. FIG. 23 shows the results obtained under these conditions using PEG-ceramide (C14:0). No fusion was observed after pre-incubation of the fusogenic LUVs with the sink for 5 minutes prior to addition of RBCs (FIG. 23, panels a and b). However, after a 1 hr pre-incubation, some fusion with RBCs was observed (FIG. 23, panels c and d), suggesting that under these conditions the PEG-ceramide could transfer out of the liposomes and became fusogenic. With longer incubations (2 hr), the pattern of fluorescent labeling changed. Rather than diffuse labeling of the RBC plasma membranes, extensive punctate fluorescence was observed (FIG. 23, panels e and f) and this pattern was maintained for up to 24 hr. The punctate fluorescence did not appear to be associated with cells and it may represent fusion of fluorescent liposomes with the sink, although previous fluorescent measurements of liposome-liposome fusion indicated that this did not occur to any appreciable extent. A second possibility is that exchange of the fluorescent probe over the longer time courses leads to labeling of the sink, although it seems unlikely that this would prevent fusion and labeling of the RBCS. When PEG-ceramide (C20:0) was used, there was no evidence for fusion after preincubation of LUVs with the sink for 5 min (FIG. 24, panels a and b), 1 hr (FIG. 24, panels c and d), 2 hr (FIG. 24, panels e and f), or for up to 24 hr (results not shown).

Detailed Description Text (98):
FIGS. 22-24 unequivocally establish that the liposomes of the present invention exhibit programmable fusion with intact cells. Firstly, liposomes composed of DOPE:cholesterol:DODAC (40:45:15) that contain no PEG-lipid fuse rapidly and extensively with RBCs. Secondly, when the liposomes contain 5 mol % PEG-lipid fusion is blocked regardless of the composition of the lipid anchor. Thirdly, in the presence of a sink to which the PEG-lipid can transfer, fusogenic activity can be restored at a rate that is dependent on the nature of the lipid anchor. Although exchange leading to fusion could not be demonstrated when the PEG-ceramide (C20:0) was used, it is believed this is a problem with the assay rather than a lack of fusogenic potential. In vivo there would be an almost infinite sink for PEG-lipid exchange.

Current US Original Classification (1):
424/450

Other Reference Publication (22):
Gao, X. and Huang, L., "Cationic liposomes and Polymers for Gene Transfer," J. Liposome Res. 3(1):17-30 (1993).

L4: Entry 43 of 68 File: USPT Apr 14, 1998

DOCUMENT-IDENTIFIER: US 5738868 A
TITLE: Liposome compositions and kits therefor

Brief Summary Text (6):
Liposome-encapsulated agents often have bio-distributions and efficiencies which differ greatly from the free agents. In particular, it is often desired to provide drugs through inhalation. The rapid systemic uptake of an agent from the site of administration in the respiratory tract can be eliminated or greatly reduced by administering it in a predominantly liposome-encapsulated form, leading to reduced toxicity and improved therapeutic action over an extended period of time.

Brief Summary Text (24):
According to further features in preferred embodiments of the invention described below, the step of dehydration includes lyophilization to form a lyophilized powder.

Brief Summary Text (25):
There is further provided in accordance with the present invention, a stable dehydrated powder of a treated liposome.

Detailed Description Text (3):
It is a particular feature of the invention that stable dehydrated powders of the prepared liposome can be prepared which can be stored for relatively long periods of time prior to rehydration and radio-labelling.

Detailed Description Text (13):
According to the present method liposomes 216, lyophilized at least once bind with between about 90% to about 95% efficiency, and with an average binding efficiency of 92%. Liposomes 216, when lyophilized a second time have been found to consistently bind to Technetium with between about 92% to about 98% efficiency and with an average binding efficiency between about 95% to about 96%. Preferably the lyophilized liposomes 216 are in powder form.

Detailed Description Text (26):
1 to 2 ml of hospital standard apirogenic 0.9% NaCl solution was injected into a vial storing 5 mg of treated liposome powder under vacuum. 30 mCi of Na-pertechnetate was added and the resultant mixture incubated at room temperature for between about 10 to 30 minutes. Between 90 and 95% binding efficiency was obtained.

Detailed Description Text (27):
It is a particular feature of the present invention that lyophilized liposomes 216 can be stored as a powder prior to labelling. It will be appreciated that storage of the powder under vacuum is preferred in order to ensure long term stability of the liposome 216. It is further appreciated that predetermined selected amounts of liposome 216 can be stored under vacuum in sealed vials to be used by a technician at the time of labelling.

Detailed Description Text (32):
More preferably the kit also includes a suitable cryo-protector which prevents change to the liposome's morphology during freeze drying, storing and reconstitution. Suitable cryo-protectors include but are not limited to sugars such as mannitol, sucrose, dextrose, and the like. Alternatively Poly Ethylene Glycol (PEG) may be also used. The labelled liposome solution is suitable for delivery to the respiratory

tract by inhalation from a liquid solution using a nebuliser. Alternatively the solution can be injected directly into the blood system. Furthermore, the solution can be injected either subcutaneously or intra-muscularly into a subject.

Detailed Description Text (33):
It is a particular feature of the present method, that diagnostic inhalation tests performed on healthy test subjects show that about 1/3 the quantity of radio-labelling agent was required as contrasted with radio-labelled liposomes formed by conventional methods of formulation.

Current US Original Classification (1):
424/450

L4: Entry 48 of 68 File: USPT Aug 5, 1997

DOCUMENT-IDENTIFIER: US 5653996 A
TITLE: Method for preparing liposomes

Detailed Description Text (7):
In certain embodiments, the liposome is sterically stabilized by the incorporation of polyethylene glycol (PEG), or by the PEG headgroups of a synthetic phospholipid (PEG conjugated to distearoyl phosphatidylethanolamine (DSPE), see e.g. the method of Papahadjopoulos et al., Proc. Natl. Acad. Sci. USA 88:11460-11464 (1991), hereby incorporated by reference.

Detailed Description Text (56):
For therapeutic use, the liposomes are placed into pharmaceutically acceptable, sterile, isotonic formulations together with required cofactors, and optionally are administered by standard means well known in the field. The formulation is preferably liquid, and is ordinarily a physiologic salt solution containing non-phosphate buffer at pH 6.8-7.6, or may be lyophilized powder. Liposomes may be formulated with pharmacologically acceptable detergents such as Tween 20 or polyethylene glycol (PEG), or with serum albumin.

Detailed Description Text (61):
It is envisioned that injections (intramuscular or subcutaneous) will be the primary route for therapeutic administration of the liposomes of this invention, intravenous delivery, or delivery through catheter or other surgical tubing is also used. Alternative routes include tablets and the like, commercially available nebulizers for liquid formulations, and inhalation of lyophilized or aerosolized liposomes. Liquid formulations may be utilized after reconstitution from powder formulations.

Detailed Description Text (62):
The liposomes of this invention may also be administered via other microparticulate delivery systems or sustained release formulations placed in certain tissues including blood. Suitable examples of sustained release carriers include semipermeable polymer matrices in the form of shaped articles, e.g. suppositories, or microcapsules. Implantable or microcapsular sustained release matrices include polylactides (U.S. Pat. Nos. 3,773,919, EP 58,481) copolymers of L-glutamic acid and gamma ethyl-L-glutamate (U. Sidman et al., Biopolymers 22(1):547-556, (1985)), poly(2-hydroxyethyl-methacrylate) or ethylene vinyl acetate (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981) and R. Langer, Chem. Tech. 12:98-105 (1982)). Pharmaceutically acceptable polymers, such as collagen, polylysine, polylactic acid, polymethylacrylate, polyurethane, polyglycolic acid, hydroxypropylcellulose, agar and agarose, are also suitable carriers for liposomes of this invention. Methods for preparing these polymers in cross-linked and/or gel form are well known, and the methods can be readily adapted to incorporate liposomes. Many of the polymers, such as agar, collagen, and polyurethanes can be formulated in permeable cross-linked structures which allow liposome movement through and out of the matrices at a selected rate. Matrices of this type are suitable for drug delivery in body cavities, where the matrix can be held in place over an extended period, or for ocular use, where an implant can take the form of a clear lens. Other polymer compositions, like polylactate, can be formulated as a biodegradable solid which releases the entrapped liposome slowly over an extended polymer degradation period. Such matrices are suitable for liposome release in the mouth or stomach. Some of the polymer compositions, such as polylysine, can be polymerized in a liposome suspension to form a polymer shell about individual liposomes, to form a coating which, for example,

would protect the liposomes from rapid breakdown in the stomach.

Detailed Description Text (71):
Aerosolized liposomes, or liposome sprays are a convenient vehicle for applying the liposomes to nasal or oral mucosa, or for delivery into the respiratory tract. In one embodiment, the liposomes are formulated as a dilute aqueous suspension and sprayed from a conventional pump or squeeze spray bottle. Alternatively, the liposomes are formulated for use with fluorocarbon propellant solvents in a pressurized canister system. Liposomes are also desirably used with nebulizing equipment. Aerosol delivery of liposomes is particularly suited for delivery of lipids and passenger molecules to the lungs, for treating a lung condition or disease. For example, lung surfactant lipids and lung surfactant-associated proteins are desirably delivered via aerosolized liposome to an infant or other individual having or at risk of having respiratory distress. The liposomes may be aerosolized under conditions which produce aerosol particle sizes favoring particle deposition in a selected region of the respiratory tract, see e.g. Radhakrishnan, U.S. Pat. No. 5,192,528.

Current US Original Classification (1):
424/450

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☐ 31. Document ID: US 5981474 A

L4: Entry 31 of 68 File: USPT Nov 9, 1999

US-PAT-NO: 5981474
DOCUMENT-IDENTIFIER: US 5981474 A

TITLE: Solubilization of pharmaceutical substances in an organic solvent and preparation of pharmaceutical powders using the same

DATE-ISSUED: November 9, 1999

INVENTOR-INFORMATION:

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US-CL-CURRENT: 514/2; 424/450, 424/489, 514/21, 530/412, 530/418, 530/419, 530/427

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 32. Document ID: US 5952312 A

L4: Entry 32 of 68 File: USPT Sep 14, 1999

US-PAT-NO: 5952312
DOCUMENT-IDENTIFIER: US 5952312 A

TITLE: NADH and NADPH therapeutic agents for nasal, sublingual, rectal and dermal administration

DATE-ISSUED: September 14, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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US-CL-CURRENT: 514/47; 424/401, 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 33. Document ID: US 5939401 A

L4: Entry 33 of 68 File: USPT Aug 17, 1999

US-PAT-NO: 5939401
DOCUMENT-IDENTIFIER: US 5939401 A

TITLE: Cationic amphiphile compositions for intracellular delivery of therapeutic molecules

DATE-ISSUED: August 17, 1999

INVENTOR-INFORMATION:

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US-CL-CURRENT: 514/44; 424/450, 514/2, 552/544

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 34. Document ID: US 5935936 A

L4: Entry 34 of 68 File: USPT Aug 10, 1999

US-PAT-NO: 5935936
DOCUMENT-IDENTIFIER: US 5935936 A

TITLE: Compositions comprising cationic amphiphiles and co-lipids for intracellular delivery of therapeutic molecules

DATE-ISSUED: August 10, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Marshall; John	Milford	MA		
Cheng; Seng H.	Wellesley	MA		
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US-CL-CURRENT: 514/44; 424/423, 424/450, 435/455, 435/458, 514/2, 552/544, 564/197

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 35. Document ID: US 5885613 A

L4: Entry 35 of 68 File: USPT Mar 23, 1999

US-PAT-NO: 5885613
DOCUMENT-IDENTIFIER: US 5885613 A

TITLE: Bilayer stabilizing components and their use in forming programmable fusogenic liposomes

DATE-ISSUED: March 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Cullis; Pieter R.	Vancouver			CA

US-CL-CURRENT: 424/450; 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 36. Document ID: US 5874062 A

L4: Entry 36 of 68 File: USPT Feb 23, 1999

US-PAT-NO: 5874062
DOCUMENT-IDENTIFIER: US 5874062 A

TITLE: Methods of computed tomography using perfluorocarbon gaseous filled

microspheres as contrast agents

DATE-ISSUED: February 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.4; 424/450, 424/489, 424/9.51, 424/9.52, 600/431

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 37. Document ID: US 5840710 A

L4: Entry 37 of 68 File: USPT Nov 24, 1998

US-PAT-NO: 5840710
DOCUMENT-IDENTIFIER: US 5840710 A

TITLE: Cationic amphiphiles containing ester or ether-linked lipophilic groups for intracellular delivery of therapeutic molecules

DATE-ISSUED: November 24, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lee; Edward R.	Quincy	MA		
Harris; David J.	Lexington	MA		
Siegel; Craig S.	Woburn	MA		
Lane; Mathieu B.	Cambridge	MA		
Hubbard; Shirley C.	Belmont	MA		
Cheng; Seng H.	Wellesley	MA		
Eastman; Simon J.	Marlboro	MA		
Marshall; John	Milford	MA		
Scheule; Ronald K.	Hopkinton	MA		

US-CL-CURRENT: 514/44; 424/450, 514/2, 554/1, 554/227, 560/1, 560/224

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 38. Document ID: US 5820848 A

L4: Entry 38 of 68 File: USPT Oct 13, 1998

US-PAT-NO: 5820848
DOCUMENT-IDENTIFIER: US 5820848 A

TITLE: Methods of preparing interdigitation-fusion liposomes and gels which encapsulate a bioactive agent

DATE-ISSUED: October 13, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Boni; Lawrence T.	Monmouth Junction	NJ		
Janoff; Andrew S.	Yardley	PA		
Minchey; Sharma R.	Monmouth Junction	NJ		
Perkins; Walter R.	Monmouth Junction	NJ		
Swenson; Christine E.	Princeton Junction	NJ		
Ahl; Patrick L.	Princeton	NJ		
Davis; Thomas S.	Valhalla	NY		

US-CL-CURRENT: 424/9.4; 264/4.1, 424/1.21, 424/450, 424/9.321, 436/829, 516/102

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 39. Document ID: US 5814666 A

L4: Entry 39 of 68 File: USPT Sep 29, 1998

US-PAT-NO: 5814666
DOCUMENT-IDENTIFIER: US 5814666 A

TITLE: Encapsulated and non-encapsulated nitric oxide generators used as antimicrobial agents

DATE-ISSUED: September 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Green; Shawn J.	Vienna	VA		
Keefer; Larry K.	Bethesda	MD		

US-CL-CURRENT: 514/611; 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 40. Document ID: US 5783565 A

L4: Entry 40 of 68 File: USPT Jul 21, 1998

US-PAT-NO: 5783565
DOCUMENT-IDENTIFIER: US 5783565 A

TITLE: Cationic amphiphiles containing spermine or spermidine cationic group for intracellular delivery of therapeutic molecules

DATE-ISSUED: July 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lee; Edward R.	Quincy	MA		
Harris; David J.	Lexington	MA		
Siegel; Craig S.	Woburn	MA		
Cheng; Seng H.	Wellesley	MA		
Eastman; Simon J.	Marlboro	MA		
Marshall; John	Milford	MA		
Scheule; Ronald K.	Hopkinton	MA		

US-CL-CURRENT: 514/44; 424/450, 516/DIG.7, 536/23.1, 552/544

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 41. Document ID: US 5770559 A

L4: Entry 41 of 68 File: USPT Jun 23, 1998

US-PAT-NO: 5770559
DOCUMENT-IDENTIFIER: US 5770559 A

TITLE: Solubilization of pharmaceutical substances in an organic solvent and preparation of pharmaceutical powders using the same

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Manning; Mark C.	Fort Collins	CO		
Randolph; Theodore W.	Niwot	CO		
Shefter; Eli	LaJolla	CA		
Falk, III; Richard F.	Boulder	CO		

US-CL-CURRENT: 514/2; 424/450, 424/489, 514/21, 530/412, 530/418, 530/419, 530/427

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 42. Document ID: US 5747059 A

L4: Entry 42 of 68 File: USPT May 5, 1998

US-PAT-NO: 5747059
DOCUMENT-IDENTIFIER: US 5747059 A

TITLE: Atrophy of skin/mucous membrane

DATE-ISSUED: May 5, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Korsgaard; Niels	V.ae butted.rl.o slashed.se			DK
Piggott; James Robertson	Bothell	WA		
Labroo; Virender Mohan	Mill Creek	WA		
Bain; Steven	Birker.o slashed.d			DK

US-CL-CURRENT: 424/451; 424/423, 424/434, 424/436, 424/447, 424/449, 424/450, 424/464, 424/DIG.15

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 43. Document ID: US 5738868 A

L4: Entry 43 of 68 File: USPT Apr 14, 1998

US-PAT-NO: 5738868
DOCUMENT-IDENTIFIER: US 5738868 A

TITLE: Liposome compositions and kits therefor

DATE-ISSUED: April 14, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shinkarenko; Leonid Lurya	Rehovot			IL

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 264/4.6, 424/1.21, 424/9.321

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 44. Document ID: US 5733572 A

L4: Entry 44 of 68 File: USPT Mar 31, 1998

US-PAT-NO: 5733572
DOCUMENT-IDENTIFIER: US 5733572 A

TITLE: Gas and gaseous precursor filled microspheres as topical and subcutaneous delivery vehicles

DATE-ISSUED: March 31, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Matsunaga; Terry O.	Tucson	AZ		
Yellowhair; David	Tucson	AZ		

US-CL-CURRENT: 424/450; 424/1.21, 424/489, 424/9.321, 424/9.4, 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 45. Document ID: US 5720950 A

L4: Entry 45 of 68 File: USPT Feb 24, 1998

US-PAT-NO: 5720950
DOCUMENT-IDENTIFIER: US 5720950 A

TITLE: Polymers containing antifibrotic agents, compositions containing such polymers, and methods of preparation and use

DATE-ISSUED: February 24, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Poiani; George J.	Jamesburg	NJ		
Riley; David J.	New Brunswick	NJ		
Liao; Wei-Chi	Princeton Junction	NJ		
Kahn; Joachim	Highland Park	NJ		
Gean; Keria Fiorella	Highland Park	NJ		

US-CL-CURRENT: 424/78.29; 424/450, 424/78.08, 424/78.17, 424/78.3, 514/824, 525/418, 528/288, 528/300, 528/422, 528/425

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 46. Document ID: US 5719131 A

L4: Entry 46 of 68 File: USPT Feb 17, 1998

US-PAT-NO: 5719131
DOCUMENT-IDENTIFIER: US 5719131 A

TITLE: Cationic amphiphiles containing dialkylamine lipophilic groups for intracellular delivery of therapeutic molecules

DATE-ISSUED: February 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Harris; David J.	Lexington	MA		
Lee; Edward R.	Quincy	MA		
Siegel; Craig S.	Woburn	MA		
Cheng; Seng H.	Wellesley	MA		
Eastman; Simon J.	Marlboro	MA		
Marshall; John	Milford	MA		
Scheule; Ronald K.	Hopkinton	MA		

US-CL-CURRENT: 514/44; 424/450, 516/DIG.7, 552/544

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 47. Document ID: US 5660822 A

L4: Entry 47 of 68 File: USPT Aug 26, 1997

US-PAT-NO: 5660822
DOCUMENT-IDENTIFIER: US 5660822 A

TITLE: Polymers containing antifibrotic agents, compositions containing such polymers, and methods of preparation and use

DATE-ISSUED: August 26, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Poiani; George J.	Jamesburg	NJ		
Riley; David J.	New Brunswick	NJ		
Liao; Wei-Chi	Princeton Junction	NJ		
Kahn; Joachim	Highland Park	NJ		
Gean; Keria Fiorella	Highland Park	NJ		

US-CL-CURRENT: 424/78.17; 424/450, 514/824, 514/838

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 48. Document ID: US 5653996 A

L4: Entry 48 of 68 File: USPT Aug 5, 1997

US-PAT-NO: 5653996
DOCUMENT-IDENTIFIER: US 5653996 A

TITLE: Method for preparing liposomes

DATE-ISSUED: August 5, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hsu; Chung C.	Los Altos Hills	CA		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 49. Document ID: US 5643599 A

L4: Entry 49 of 68 File: USPT Jul 1, 1997

US-PAT-NO: 5643599
DOCUMENT-IDENTIFIER: US 5643599 A

TITLE: Intracellular delivery of macromolecules

DATE-ISSUED: July 1, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lee; Kyung-Dall	Providence	RI		
Portnoy; Daniel A.	Philadelphia	PA		
Swanson; Joel A.	Brookline	MA		

US-CL-CURRENT: 424/450; 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 50. Document ID: US 5595756 A

L4: Entry 50 of 68 File: USPT Jan 21, 1997

US-PAT-NO: 5595756
DOCUMENT-IDENTIFIER: US 5595756 A

TITLE: Liposomal compositions for enhanced retention of bioactive agents

DATE-ISSUED: January 21, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bally; Marcel B.	Bowen Island			CA
Boman; Nancy L.	Richmond			CA
Cullis; Pieter R.	Vancouver			CA
Mayer; Lawrence D.	North Vancouver			CA

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 51. Document ID: US 5512294 A

L4: Entry 51 of 68 File: USPT Apr 30, 1996

US-PAT-NO: 5512294
DOCUMENT-IDENTIFIER: US 5512294 A

TITLE: Targeted polymerized liposome contrast agents

DATE-ISSUED: April 30, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Li; King C.	Stanford	CA	94305	
Bednarski; Mark D.	Los Altos	CA	94024	
Storrs; Richard W.	Union City	CA	94587	
Li; Henry Y.	Visalia	CA	93277	
Trooper; Francois D.	Oakland	CA	94611	
Song; Curtis K. H.	Sunnyvale	CA	94086	
Sipkins; Dorothy A.	Palo Alto	CA	94301	
Kuniyoshi; Jeremy K.	Cupertino	CA	95014	

US-CL-CURRENT: 424/450; 424/1.21, 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 52. Document ID: US 5399331 A

L4: Entry 52 of 68 File: USPT Mar 21, 1995

US-PAT-NO: 5399331
DOCUMENT-IDENTIFIER: US 5399331 A

TITLE: Method for protein-liposome coupling

DATE-ISSUED: March 21, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Loughrey; Helen C.	Vancouver			CA
Cullis; Pieter R.	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Choi; Lewis S.	Burnaby			CA

US-CL-CURRENT: 424/450; 424/417, 424/418

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 53. Document ID: US 5384128 A

L4: Entry 53 of 68 File: USPT Jan 24, 1995

US-PAT-NO: 5384128
DOCUMENT-IDENTIFIER: US 5384128 A

TITLE: Method of and compounds for treatment for cystic fibrosis

DATE-ISSUED: January 24, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Meezan; Elias	Birmingham	AL		
Wang; Rongxiang	Birmingham	AL		

US-CL-CURRENT: 424/450; 424/436, 424/449, 424/45, 424/451, 424/464, 436/829, 514/937, 514/962, 514/963

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 54. Document ID: US 5334391 A

L4: Entry 54 of 68 File: USPT Aug 2, 1994

US-PAT-NO: 5334391
DOCUMENT-IDENTIFIER: US 5334391 A

TITLE: Intracellularly cleavable compounds

DATE-ISSUED: August 2, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Clark; Brian R.	Redwood City	CA		
Nag; Bishwajit	Pacifica	CA		

US-CL-CURRENT: 424/450; 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 55. Document ID: US 5298488 A

L4: Entry 55 of 68 File: USPT Mar 29, 1994

US-PAT-NO: 5298488
DOCUMENT-IDENTIFIER: US 5298488 A

TITLE: CM-chitin derivatives and use thereof

DATE-ISSUED: March 29, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kojima; Masayoshi	Minami-Ashigara			JP
Komazawa; Hiroyuki	Kanagawa			JP

US-CL-CURRENT: 514/8; 424/450, 530/322, 530/345

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 56. Document ID: US 5288499 A

L4: Entry 56 of 68 File: USPT Feb 22, 1994

US-PAT-NO: 5288499
DOCUMENT-IDENTIFIER: US 5288499 A

TITLE: Sterodial liposomes

DATE-ISSUED: February 22, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Janoff; Andrew S.	Yardley	PA		
Popescu; Mircea C.	Plainsboro	NJ		
Weiner; Alan L.	Lawrenceville	NJ		
Bolcsak; Lois E.	Lawrenceville	NJ		
Tremblay; Paul A.	Hamilton	NJ		
Swenson; Christine E.	Princeton Junction	NJ		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.6, 424/1.21, 424/9.4, 428/402.2, 436/829, 514/167, 514/78, 514/887, 514/967

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 57. Document ID: US 5171578 A

L4: Entry 57 of 68 File: USPT Dec 15, 1992

US-PAT-NO: 5171578
DOCUMENT-IDENTIFIER: US 5171578 A

TITLE: Composition for targeting, storing and loading of liposomes

DATE-ISSUED: December 15, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bally; Marcel B.	Vancouver			CA
Loughrey; Helen	Vancouver			CA
Cullis; Pieter R.	Vancouver			CA

US-CL-CURRENT: 424/450; 264/4.1, 436/547, 436/548, 436/829, 514/2, 514/21, 514/8, 530/391.1, 530/402, 530/812

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 58. Document ID: US 5141674 A

L4: Entry 58 of 68 File: USPT Aug 25, 1992

US-PAT-NO: 5141674
DOCUMENT-IDENTIFIER: US 5141674 A

TITLE: Methods of preparing pro-liposome dispersions and aerosols

DATE-ISSUED: August 25, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Leigh; Steven	London			GB

US-CL-CURRENT: 516/1; 264/4.1, 424/40, 424/45, 424/450, 424/47, 427/213.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 59. Document ID: US 5100662 A

L4: Entry 59 of 68 File: USPT Mar 31, 1992

US-PAT-NO: 5100662
DOCUMENT-IDENTIFIER: US 5100662 A

TITLE: Steroidal liposomes exhibiting enhanced stability

DATE-ISSUED: March 31, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bolcsak; Lois E.	Lawrenceville	NJ		
Boni; Lawrence	Monmouth Junction	NJ		
Popescu; Mircea C.	Plainsboro	NJ		
Tremblay; Paul A.	Hamilton	NJ		

US-CL-CURRENT: 424/450; 424/208.1, 424/210.1, 424/211.1, 424/226.1, 424/227.1, 424/228.1, 424/250.1, 424/272.1, 424/277.1, 424/283.1, 424/85.2, 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 60. Document ID: US 5059421 A

L4: Entry 60 of 68 File: USPT Oct 22, 1991

US-PAT-NO: 5059421
DOCUMENT-IDENTIFIER: US 5059421 A

TITLE: Preparation of targeted liposome systems of a defined size distribution

DATE-ISSUED: October 22, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Loughrey; Helen C.	Vancouver			CA
Cullis; Pieter R.	Vancouver			CA
Bally; Marcel B.	Bowen Island			CA
Choi; Lewis S. L.	Burnaby			CA
Wong; Kim F.	Vancouver			CA

US-CL-CURRENT: 424/417; 264/4.3, 424/418, 424/450, 435/4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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L4: Entry 67 of 68 File: USPT Jun 13, 1989

DOCUMENT-IDENTIFIER: US 4839175 A
TITLE: Liposomes with enhanced retention on mucosal tissue

Abstract Text (1):
A liposome composition designed for enhanced binding to mucosal tissue, The liposomes contain about 10-40 mole percent of an amine-derivatized lipid component in which a charged amine group is spaced from a lipid polar head region by a carbon-containing spacer arm at least 3 atoms in length. The liposomes preferably have a close packed lipid structure produced by inclusion of between 20-50 mole percent of cholesterol or an amine-derivatized cholesterol, and/or phospholipids with predominantly saturated acyl chain moieties. For ophthalmic use, the liposomes may be suspended in an aqueous medium containing a high-viscosity polymer, to enhance further the retention of liposomes on a corneal surface.

Brief Summary Text (32):
The retention of a solution-form drugs on the corneal surface can be enhanced by the use of polymers. such as hydroxythylcellulose or methylcellulose, which increase the viscosity of the drug solution. Polymer containing viscous liquids are used, for example, in the treatment of dry eye, to help keep the corneal surface moist. However, with the increased viscosity, very little of the originally applied liquid is retained for more than about an hour, so frequent dosing is necessary.

Brief Summary Text (51):
The liposome composition may further be formulated for increase retention near the tissue site (as well as increased retention to the mucosal tissue). For ophthalmic uses, the formulation may include increase-viscosity polymers. For uses in body cavities, the liposome may be formulated for delayed release in suppositories or slow-release polymer matrices. Aerosolized liposomes for nasal and oral drug deliverly, and cream or foam formulations for topical application are also disclosed.

Brief Summary Text (53):
In still another aspect, the invention includes a method of treating dry-eye, by applying to the ocular surface, a preferably optically clear suspension of positively charged liposomes of the type described above. The suspension may contain increased-viscosity polymers for greater liposome retention at the ocular site. The liposomal lipids contribute to the lubricating properties of the dry-eye composition.

Drawing Description Text (7):
FIG. 6 shows the retention on an ocular tissue of liposomes prepared with either lysine PE (circles) or lysine lysinyl PE (triangles), in a suspension containing either buffer (closed symbols) or polymers (open symbols): and

Drawing Description Text (8):
FIG. 7 shows the retention on an ocular tissue of liposomes prepared with either lysinyl PE, at 20 (open circles) or 30 (closed circles) mole percent, or lysine lysinyl PE, at 10 (open triangles) or 20 (closed triangles) mole percent, in a suspension containing a polymer additive, and neutral liposomes with (closed squares) or without polymer additive (open squares).

Detailed Description Text (55):

Several studies referred to above, and described in Examples VII-XI, demonstrates the enhanced binding of the liposomes of the invention to ocular tissue. It is likely that the enhanced retention of liposomes to mucosal epithelium involves electrostatic binding of the positively charged liposomes to mucin, a negatively charged glycoprotein which is produced by the goblet cells of the conjunctiva, and which remains bound to the epithelium. Since all other mucosal tissue types, including nasal, oral, vaginal, rectal, and gastrointestinal mucosa, are characterized by epithelial cells which produce a cell-bound mucin, it is expected that the liposomes of the invention would show enhanced retention to all mucosal tissue types. The studies reported in Examples XII verify that a significantly enhanced liposome retention is seen with a variety of other tissue types, including trachea, esophagus, stomach, small intestine, and rectum. The study compared the binding to the tissue of uncharged liposomes with liposomes containing either 20 mole percent stearylamine or 20 mole percent lysine lysinyl PE. As summarized in Table VI of Example XII, both positively charged liposome preparations showed enhanced adhesion to most of the mucosal tissue type compared to the adhesion of the neutral liposomes. Lys-lys-PE liposomes showed twice the percent adhsesion to the trachea, esophagus and small intestine and a lesser but significant enhanced adhesion to the stomach and rectum relative to the stearylamine containing liposomes.

Detailed Description Text (59):
As indicated above, the retention of liposomes on mucosal tissue can be enhanced by including in the suspension, high molecular weight polymers which act to increase suspension viscosity. Typical polymers for use in ophthalmic formulations are methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and polyvinylalcohol. The effect of these polymers on ocular retention wsa examined in the studies reported in Example XI. In a first study, SUVs prepared with either 20 mole lysinyl PE or lysine lysinyl PE were formulated in a dilute suspension of buffer alone or buffer containing 0.8% hydroxyethylcellulose and 0.2% polyvinylalcohol, and ocular retention over a 1 hour period was measured. As may be seen, addition of polymers (solid symbols) significantly increased the level of liposome retention after 1 hour in both lysinyl PE SUvs (circles) and in lysine lysinyl PE SUVs (triangles).

Detailed Description Text (60):
A second study examined the effect of the Neo-Tears.TM. polymer (a product of Barnes Hind, Sunnyvale, CA) on retention of SUVs having a variety of lipid compositions. Interestingly, the polymers enhanced the retention of uncharged liposomes only slightly (closed squares vs open squares), in contrast to the effect seen in FIG. 6 for charged SUVs. The other data plots in FIG. 7 show retention of polymer solutions of SUVs containing different concentrations of lysinyl PE (circles) and lysine lysinyl PE (triangles).

Detailed Description Text (64):
Conventional dry eye formulations are polymer solutions which provide, when applied to drop form, a film of moisture which has increased retention on the eye by virtue of the solution viscosity. The liposome formulation of the present invention provides three important advantages over these earlier formulations. First, the liposomes in the suspension are retained on the eye in appreciable quantity for several hours, in contrast to viscous solutions which are largely cleared after 1 hour. Second, the surface-bound liposomes provide a matrix for holding encapsulated and bound aqueous fluid. Third, the liposomes themselves can be formulated to supply necessary lipids needed for film formation. Long-chain alcohols and fatty acids, and cholesterol esters which make up the films are all compatible with stable vesicular structures. Further, experiments conducted in support of the present invention indicated that the aqueous ocular environment contains phospholipases capable of deacylating phospholipids to yield long-chain fatty acids.

Detailed Description Text (68):
Still another consideration is achieving good optical clarity in a liposome/polymer suspensions. In addition to liposome size, which is discussed above, the liposomes and polymers must be stable in terms of aggregate effects, such that if aggregation occurs, the liposome/polymer complexes can be easily dispersed by shaking. For both of the hydroxyethylcellulose/polyvinylalcohol, and NEO-TEARS.TM. polymers used in formulating ophthalmic liposomes, good optical clarity after two months storage at room temperature, and clouding which was observed could be cleared by moderate

shaking.

Detailed Description Text (70):
Aerosolized liposomes, or liposome sprays are a convenient vehicle for applying the liposomes to the nasal or oral mucosa. In one simple embodiment, the liposomes are formulated as a dilute aqueous suspension, and sprayed from a conventional pump or squeeze spray bottle. In more elaborate embodiments, the liposomes are formulated for use with flurocarbon propellant solvents in a pressurized cannister system. Several liposome formulations which are suitable for use with propellant solvents are disclosed in co-owned U.S. Patent Application for "Lipsome Inhalation System and Method", Ser. No. 737,221, filed May 22, 1985 and now abandoned, and PCT Patent Application No. PCT/US86/01095 for "Lipsome Inhalation System and Method", filed May 22, 1986, which applications are incorporated by reference herein. Briefly, the liposomes may be suspended in the propellant in powdered or aqueous paste form, or combined in paste or powdered form with the propellant during propellant release from the pressurized cannister.

Detailed Description Text (79):
Biocompatible polymers, such as collagen, polylysine, polylactic acid, polymethyacrylate, polyurethanes, polyglycolic acid, hydroxypropylcellulose, agar and agarose, are also suitable bulk carriers for the liposomes of the invention. Methods for preparing these polymers in cross-linked and/or gel form are well known, and the methods can be readily adapted to incorporate liposomes, again with the proviso that transient temperatures above about 60 C. are avoided. Many of the polymers, such as agar, collagen, and polyurethanes can be formulated in permeable cross-linked structures which allow liposome movement through and out of the matrices at a selected rate. Matrices of this type are suitable for drug delivery in body cavities, where the matrix can be held in place over an extended period, or for ocular use, where the implant can take the form of a clear lens or the like. Other polymer compositions, like polylactate, can be formulated as a biodegradable solid which release the entrapped slowly over an extended polymer degradation period. Such matrices are suitable for liposome release in the mouth or stomach. Some of the polymer compositions, such as polylysine, can be polymerized in a liposome suspension to form a polymer shell about individual liposomes, to form a coating which, for example, would protect the liposomes from rapid breakdown in the stomach.

Detailed Description Text (82):
In another therapeutic use, the enhanced-retention liposomes provide several advantages over polymer solutions for treating dry eye.

Detailed Description Text (181):
In vivo ocular retention studies were performed in rabbit eyes using a scintillation probe technique. In each experiment, 10 .mu.l of liposomes containing about 100 nmole lipids and 10.sup.5 cpm of .sup.125 I-labeled PE were applied to the rabbit eye. Retention was assessed with the gamma probe positioned over the eye. A constant distance between the probe and the eye of 2 cm was insured by fitting the probe into a plexiglas sleeve-holder. A 1/8 inch thick lead partition placed against the lacrimal-nasal region of the rabbit effectively blocked radioactive material which drained into the nasolacrimal region. Retention time was monitored over a period of 1 hour unless specified otherwise. From the chart recordings, peak height readings were obtained. Total radioactivity of each reading was calculated from a standard curve by in vitro measurements of standard dilutions of the radioactive liposomes. Percent retention was calculated based on counts per minute (CPM) of the original 10 .mu.l sample.

Detailed Description Text (195):
Ocular Retention-Effect of Polymer Additives

Detailed Description Text (196):
In a first study, SUVs containing egg PC: lysinyl PE, 80:20 were mixed with equal volumes of either phosphate buffer (control) or a polymer solution containing 0.8% hydroxyethylcellulose and 0.2% polyvinylalcohol. Both compositions showed about 20% retention of labelled lipid counts after 1 hour, showing that the polymers produce very little improvement in ocular retention in non-cholesterol SUVs.

Detailed Description Text (197):
In a second study, SUVS composed of 40 mole percent egg PC, 40 mole percent cholesterol, and 20 mole percent of either lysinyl PE or lysine lysinyl PE were mixed with either the phosphate buffer of the polymer solution. All four preparations were tested for ocular retention as in Example VIII. The results are shown in FIG. 6. The lowest retention was seen for the control lysinyl PE SUVs (solid circles). Addition of polymer solution to the lysinyl PE SUVs (open circles) increased retention time nearly twofold after 1 hour. The control lysine lysinyl PE SUVs (closed triangles) gave substantially higher retention than either of the lysine PE preparations, and retention was enhanced still further by the presence of the polymer. A comparison of the the two studies indicate that (a) polymers can enhance the ocular binding of amine-derivatized liposomes, and (b) the enhancement requires the presence of cholesterol in the liposomes.

Detailed Description Text (198):
A third study examined the effects of Neo-Tears.TM., a commercial ocular polymer solution on ocular retention of SUVs containing either lysinyl PE (20 or 30 mole percent) or lysine lysinyl PE (10 or 20 mole percent). A control preparation contained 20 mole percent PE. The SUVs all contained 40 mole percent cholesterol and remainder egg PC. The polymer solution was mixed with an equal volume of each SUV preparation.

Detailed Description Text (199):
The ocular retention over a 1 hour period of the polymer/SUV preparations is shown in FIG. 7. The two low-retention curves are for control SUVs with (solid squares) and without (open squares) the polymer. Thus the polymer provides some improvement, even in the absence of charge effects. The two lysinyl PE SUVs gave the retention plots indicated by the open and closed circles (20 and 30 mole percent lysinyl PE, respectively). The two lysine lysinyl PE SUVs gave the retention plots indicated by the open and closed triangles (10 and 20 mole percent lysine lysinyl PE, respectively). A comparison of the retention values for the lysinyl and lysine lysinyl SUVs in Neo-Tears vs no added polymer (FIG. 1 and 2) indicates that the polymer solution enhances retention of amine-derivatized SUVs.

Current US Original Classification (1):
424/450

CLAIMS:

7. The method of claim 1, for use in enhancing the binding of the liposomes to an ocular surface, wherein the liposomes are contained in a suspension of high molecular weight polymer at a polymer concentration which increases the viscosity of the suspension.

10. The method of claim 8, wherein the liposomes are contained in a suspension medium containing polymers selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinyl pyrrolidone, and polyvinylalcohol.

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Search Results - Record(s) 61 through 68 of 68 returned.

☐ 61. Document ID: US 5049389 A

L4: Entry 61 of 68 File: USPT Sep 17, 1991

US-PAT-NO: 5049389
DOCUMENT-IDENTIFIER: US 5049389 A

TITLE: Novel liposome composition for the treatment of interstitial lung diseases

DATE-ISSUED: September 17, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Radhakrishnan; Ramachandran	Fremont	CA		

US-CL-CURRENT: 424/450; 264/4.1, 424/434

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 62. Document ID: US 5047245 A

L4: Entry 62 of 68 File: USPT Sep 10, 1991

US-PAT-NO: 5047245
DOCUMENT-IDENTIFIER: US 5047245 A

TITLE: Novel composition for targeting, storing and loading of liposomes

DATE-ISSUED: September 10, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bally; Marcel B.	Vancouver			CA
Loughrey; Helen	Vancouver			CA
Gullis; Pieter R.	Vancouver			CA

US-CL-CURRENT: 424/450; 264/4.6, 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 63. Document ID: US 5043165 A

L4: Entry 63 of 68 File: USPT Aug 27, 1991

US-PAT-NO: 5043165
DOCUMENT-IDENTIFIER: US 5043165 A

TITLE: Novel liposome composition for sustained release of steroidal drugs

DATE-ISSUED: August 27, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Radhakrishnan; Ramachandran	Fremont	CA		

US-CL-CURRENT: 424/450; 514/180

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 64. Document ID: US 4906476 A

L4: Entry 64 of 68 File: USPT Mar 6, 1990

US-PAT-NO: 4906476
DOCUMENT-IDENTIFIER: US 4906476 A

TITLE: Novel liposome composition for sustained release of steroidal drugs in lungs

DATE-ISSUED: March 6, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Radhakrishnan; Ramachandran	Fremont	CA		

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 65. Document ID: US 4891208 A

L4: Entry 65 of 68 File: USPT Jan 2, 1990

US-PAT-NO: 4891208
DOCUMENT-IDENTIFIER: US 4891208 A

TITLE: Steroidal liposomes

DATE-ISSUED: January 2, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Janoff; Andrew S.	Yardley	PA		
Popescu; Mircea C.	Plainsboro	NJ		
Weiner; Alan L.	Plainsboro	NJ		
Bolscak; Lois E.	Lawrenceville	NJ		
Tremblay; Paul A.	Hamilton	NJ		
Swenson; Christine E.	Plainsboro	NJ		

US-CL-CURRENT: 424/1.21; 264/4.1, 264/4.6, 424/450, 424/9.4, 424/9.6, 428/402.2, 436/829, 514/167, 514/3, 514/396, 514/78, 514/885, 514/887, 514/967, 604/891.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 66. Document ID: US 4885172 A

L4: Entry 66 of 68 File: USPT Dec 5, 1989

US-PAT-NO: 4885172
DOCUMENT-IDENTIFIER: US 4885172 A

TITLE: Composition for targeting, storing and loading of liposomes

DATE-ISSUED: December 5, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bally; Marcel B.	Vancouver			CA
Loughrey; Helen	Vancouver			CA
Cullis; Pieter R.	Vancouver			CA

US-CL-CURRENT: 424/417; 264/4.3, 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 67. Document ID: US 4839175 A

L4: Entry 67 of 68 File: USPT Jun 13, 1989

US-PAT-NO: 4839175
DOCUMENT-IDENTIFIER: US 4839175 A

TITLE: Liposomes with enhanced retention on mucosal tissue

DATE-ISSUED: June 13, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Guo; Luke S. S.	Lafayette	CA		
Redemann; Carl T.	Walnut Creek	CA		
Radhakrishnan; Ramachandran	Palo Alto	CA		
Yau-Young; Annie	Los Altos	CA		

US-CL-CURRENT: 424/450; 264/4.3, 424/1.21, 424/427, 424/428, 428/402.2, 514/912, 514/914, 514/966

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 68. Document ID: US 4721612 A

L4: Entry 68 of 68 File: USPT Jan 26, 1988

US-PAT-NO: 4721612
DOCUMENT-IDENTIFIER: US 4721612 A

TITLE: Steroidal liposomes

DATE-ISSUED: January 26, 1988

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Janoff; Andrew S.	Yardley	PA		
Popescu; Mircea C.	Plainsboro	NJ		
Weiner; Alan L.	Plainsboro	NJ		
Bolcsak; Lois E.	Lawrenceville	NJ		
Tremblay; Paul S.	Hamilton	NJ		

US-CL-CURRENT: 424/1.21; 264/4.1, 264/4.6, 424/450, 424/9.4, 424/9.6, 428/402.2, 436/52, 436/829, 514/167, 514/78, 514/887, 514/967

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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DATE: Wednesday, September 04, 2002

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	DB=USPT,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR		
L4	L3 and ((424/450)!.CCLS.)	68	L4
L3	L2 and (starch or polymer or polymers or peg)	606	L3
L2	L1 and powder$	712	L2
L1	liposome$ same (nasal or inhal$)	1096	L1

END OF SEARCH HISTORY